2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ATRAZINE IN THE UNITED STATES

Atrazine is a white, odorless powder (when pure) that is used as an herbicide to stop the growth of broadleaf and grassy weeds in crops such as corn, sugarcane, sorghum, pineapples, and macadamia nuts. It is not found naturally in the environment. It is moderately soluble in water, but is more soluble in organic solvents such as acetone, chloroform, and ethyl acetate. More than 37,000 tons of atrazine were used in agricultural and weed control settings in the United States in 1997.

Atrazine is released to the environment during its production and use, with the vast majority being released as a result of its application to soils as an herbicide. Some of the applied atrazine will persist for a moderate amount of time in the soils, but some will volatilize into the atmosphere, and some will migrate out of the soil dissolved in water. In the latter case, atrazine may migrate out of the soil either in surface runoff to streams, rivers, or lakes, or it may migrate deeper into the soil and become associated with groundwater.

Atrazine will have different fates in soil, air, or water. Atrazine that remains in the soil is degraded at a moderate rate, with half-lives ranging from a few weeks to a few to several months. Relatively large amounts of atrazine (2.4–14%), however, may volatilize from the soils into the atmosphere. In the atmosphere, no direct photolysis degradation of atrazine is expected to occur, but it is expected to undergo oxidation in the presence of hydroxyl radicals. The half-life of this reaction is estimated to be 14 hours. Most of the atrazine found in the atmosphere, however, is expected to be sorbed to particulates, and this form will have a longer half-life. In this form, it can be transported significant distances in the atmosphere, and has been detected >180 miles from the nearest application site.

Atrazine is also removed from soils by runoff into bodies of water and by percolation into the soil. Atrazine has been detected in most bodies of water in regions where it has been applied as an herbicide. In these bodies of water, it is degraded very slowly; observed half-lives in surface waters are very long, generally >200 days. The atrazine that migrates into the soil and into groundwater is expected to be persistent, as no significant degradation of atrazine has been observed in groundwater. This persistence, along with its widespread usage, may explain why atrazine is detected in groundwater more frequently than other pesticides.

The general population may be exposed to atrazine found in water or air, but it is rarely found in foods. When the general population is exposed to atrazine, exposure is expected to be in the low ppb range. In a 1990 report, atrazine concentrations in drinking water from community drinking water wells ranged from 0.12 to 0.92 ppb. The highest level of atrazine detected in that survey was for a rural domestic drinking water well, in which 7 ppb of atrazine was detected. In Canada, drinking water analysis of agroeco-systems between 1987 and 1991 showed atrazine concentrations ranging from 0.05 to 0.65 ppb, with an average concentration of 0.16 ppb. Air concentrations of atrazine vary with application season; concentrations usually range from just above the detection limit of approximately 0.03 $\mu g/m^3$ (0.003 ppb) to 0.20–0.32 $\mu g/m^3$ (0.023–0.036 ppb) during the application period. The concentrations of atrazine detected in foods were low (0.001–0.028 ppm) in the few samples where it was detected.

It is not known if exposure of children to atrazine differs from that of adults. Atrazine is found in some dusts on home surfaces and in dusts on carpets, primarily in regions where atrazine is used on crops. Therefore, young children may be exposed by crawling or playing on floors. Children may also intentionally or unintentionally ingest soil, which may contain low levels of atrazine.

Populations residing near crops where atrazine is applied or hazardous waste disposal sites or manufacturing and processing plants may be exposed to higher than average levels of atrazine in ambient air or drinking water. As mentioned above, atrazine is mobile in soils and has been detected in a high percentage of the drinking water wells near crops where atrazine has been used. Atrazine has also been identified in at least 20 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for atrazine is not known.

Occupational exposures to atrazine can occur through skin contact and by inhalation of vapors and dust during its manufacture, formulation, and application. According to the United States National Occupational Exposure Survey performed between 1981 and 1983, approximately 1,000 chemical industry workers, 123 of which are female, were potentially exposed to atrazine.

2.2 SUMMARY OF HEALTH EFFECTS

Data regarding the health effects of atrazine in humans are limited to a few ecological and cohort studies that show possible links between atrazine use or exposure and increased risk of intrauterine growth retardation or increased pre-term delivery and miscarriage and one case report showing contact dermatitis following exposure to atrazine and another herbicide. The lack of information on exposure levels and the

concomitant exposure to other pesticides makes these three studies inadequate to assess the contribution of atrazine to these effects. Oral exposure studies in animals make up the bulk of the available toxicity data. The endocrine/reproductive system and the developing organism are the primary targets of atrazine toxicity. A number of studies have shown that atrazine disrupts estrus cyclicity in rats and pigs, usually accompanied by altered plasma estrogen and/or progesterone levels. These effects are thought to be due to interference of the gonadal-hypothalamic-pituitary axis and are species-specific. Developmental effects have been observed following pre-gestational, gestational, and lactational exposure of rat and rabbit dams to atrazine. The observed effects included postimplantation losses, decreases in fetal body weight, incomplete ossification, neurodevelopmental effects, and impaired development of the reproductive system.

Studies in animals have shown that atrazine can also cause damage to the heart, liver, and kidneys.

Several ecological and population-based studies have shown possible associations between atrazine usage or exposure and brain, testis, and prostate cancers and leukemia, stomach cancer, increased incidence of uterine adenocarcinoma and leukemia/lymphoma, and non-Hodgkin's lymphoma. Specific exposure data were lacking in these studies and exposure to other chemicals confounded the interpretation of the data. Animal studies have shown increased incidence of uterine adenocarcinoma and leukemia/lymphoma, mammary tumors, and lymphoma. IARC has classified atrazine as "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate evidence in humans and sufficient evidence in experimental animals.

Reproductive Effects. Animal studies have shown that atrazine disrupts estrus cyclicity and alters plasma hormone levels in rats and pigs. These effects appear to be mediated by changes in the gonadal-hypothalamic-pituitary axis that are species-, and even strain-, specific. In Sprague-Dawley rats, atrazine accelerates the normal process of reproductive senescence, which is initiated by a failure of the hypothalamus to release levels of gonadotropin releasing hormone (GnRH) that are adequate to stimulate the pituitary to release luteinizing hormone (LH). Without sufficient LH, ovulation does not occur, estrogen levels remain high, and persistent estrus results. In other strains of rats, atrazine causes elevated progesterone levels, which leads to pseudopregnancy and persistent diestrus. The mechanism of reproductive senescence in humans does not involve disruption of hormonal regulation, but is initiated by depletion of ova in the ovaries, which ultimately results in decreased plasma estrogen levels. Therefore, disruption of the menstrual cycle or acceleration of reproductive senescence is not anticipated to occur in humans as a result of atrazine exposure.

Developmental Effects. Developmental effects in response to atrazine have been demonstrated in laboratory animals. Incomplete ossification of the skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges were observed in the offspring of Sprague-Dawley rats exposed by gavage on gestational days 6–15. In rabbits exposed on gestational days 7–19, increased resorptions/litter and postimplantation losses/litter, and decreased live fetuses/litter were observed, as well as decreased fetal body weights and nonossification of forepaw metacarpals and middle phalanges, hindpaw talus and middle phalanges, and patella in the offspring. However, these effects were probably due to severe maternal toxicity. No developmental effects were noted in a two-generation study in which rats were exposed to atrazine in the diet. Female offspring of Fischer rat dams exposed to atrazine 4 weeks prior to mating had increased spontaneous activity at 70 days of age, and male offspring had improved performance (decreased latency and increased avoidance) in avoidance conditioning trials. Adult male offspring of Wistar rat dams exposed to atrazine on lactational days 1–4 had increased incidence and severity of inflammation of the lateral prostate, increased myeloperoxidase levels in the prostate, and increased total DNA in the prostate. These are thought to be indirect effects mediated by a lack of prolactin release in the dam in response to pup suckling.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Information on the toxicity of inhaled atrazine is sparse. A cohort study of farm operators and farm couples attempting to conceive showed no correlation between atrazine exposure/pesticide use and decreased fecundity. However, analysis of data regarding pesticide exposure from 1,898 farm couples living year-round on farms indicated an association between atrazine use on crops or in the yard and an increase in preterm delivery (odds ratios [OR]=2.4, 95% confidence interval [CI]=0.8–7.0 and OR=4.9, CI=1.6–15, respectively), and a weaker association with miscarriage (OR=1.5, 95% CI=0.9–2.4 and OR=1.2, CI=0.6–2.3, respectively). No exposure levels were available in these studies. In the absence of reliable data, no acute-, intermediate-, or chronic-duration inhalation MRLs were derived.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to atrazine.

The acute-duration oral MRL was based on a no-observed-adverse-effect level (NOAEL) of 1 mg/kg/day for decreased body weight gain in pregnant rabbits exposed to atrazine on gestational days 7–19 and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). In this study, groups of female New Zealand White rabbits were artificially inseminated (gestational day 0) and administered 0, 1, 5, or 75 mg/kg/day atrazine (Aatrex) in 3% aqueous corn starch containing 0.5% Tween 80 by gavage on gestational days 7–19. Slight, but statistically significant, reductions in food consumption and body weight gain were noted in the 5 mg/kg/day group. Other clinical signs related to treatment were limited to the 75 mg/kg/day group, and included increased incidence of stool variations (little, no, or soft stool), bloody vulva, and decreased absolute, but not relative, liver weight. Food consumption and body weight gain were severely reduced during the treatment period in the high dose (75 mg/kg/day) group, but rebounded after cessation of treatment; however, overall body weight gain corrected for weight of the uterus, placentas, and fetuses was significantly reduced.

Other acute-duration NOAELs and lowest-observed-adverse-effect-level (LOAELs) included: LOAELs of 50 mg/kg/day or 300 mg/kg for decreased serum prolactin and LH and elevated levels of prolactin in the pituitary of ovariectomized, estrogen supplemented female Long-Evans rats exposed for 3 or 1 days, respectively; a NOAEL of 12.5 mg/kg/day (LOAEL of 25 mg/kg/day) for decreased prolactin release in response to pup suckling in lactating rats; a NOAEL of 5 mg/kg/day for serious developmental effects (LOAEL of 75 mg/kg/day for postimplantation losses, decreased fetal body weight, nonossification of forepaw metacarpals and middle phalanges, hindpaw talus and middle phalanges, and patella) in rabbits exposed on gestational days 7–19; and a NOAEL of 10 mg/kg/day (LOAEL of 70 mg/kg/day) for developmental effects (incomplete ossification of skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges) in offspring of rat dams exposed on gestational days 6–15.

Systemic and reproductive effects have been observed in animals exposed to atrazine for 15–365 days. Decreased body weight gain was seen in rats at LOAELs of 2.7 and above. Endocrine gland weights and serum and pituitary gland hormone levels were altered in rats at LOAELs as low as 6.9 mg/kg/day for 1 month and in pigs at LOAELs as low as 1 mg/kg/day for 19 days. Disrupted estrus cyclicity or anestrus was also seen in rats and pigs at the lowest LOAELs of 6.9 and 1 mg/kg/day, respectively. Anestrus, considered to be a serious effect, occurred at the lowest LOAEL; therefore, no intermediate-duration oral MRL was derived. Other NOAELs and LOAELs observed included: a LOAEL of 50 mg/kg/day (NOAEL of 5 mg/kg/day) for increased relative liver weights in Sprague-Dawley and Donryu rats; a LOAEL of 22.6 mg/kg/day for decreased body weight gain in Fischer rats; a LOAEL of 2 mg/kg/day for degeneration of a small number of myocardial fibers, mild degeneration and inflammation and mild

chronic interstitial hepatitis and subacute glomerulitis, degeneration and desquamation of proximal tubules, a 350% increase in serum gamma-glutamyl-transferase, and mild liver histological changes in pigs; a LOAEL of 33 mg/kg/day (NOAEL of 4.6 mg/kg/day) for abnormal estrus cycle in Sprague-Dawley rats; and a LOAEL of 2 mg/kg/day for ovarian histopathology, disrupted estrogen and progesterone levels, and anestrus, and ovarian cysts and disruption of estrus cyclicity.

Chronic-duration exposure of animals to atrazine also resulted in a variety of systemic effects, including hematological, hepatic, endocrine, and body weight effects, as well as reproductive effects. No chronic-duration MRL could be derived because the lowest NOAEL, 2.4 mg/kg/day (LOAEL of 26.7 mg/kg/day for decreased body weight gain in rats exposed to atrazine in the diet for life), was higher than the serious LOAEL of 1 mg/kg/day for intermediate-duration exposure. Additional LOAELs and NOAELs included: electrocardiographic changes, atrial dilatation, fluid-filled pericardium, enlarged heart; atrophy of atrial myocardium, and edema in dogs exposed to 33.65 mg/kg/day in the feed for 52 weeks (NOAEL of 4.97 mg/kg/day); decreased body weight in CD rats exposed to 25.5 mg/kg/day atrazine in feed for 12 months (NOAEL of 3.5 mg/kg/day); and a serious LOAEL of 6.9 mg/kg/day for increased length of estrus in Sprague-Dawley rats exposed to atrazine in the diet for 18 months.